More questions raised about iPS cells safety

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Much has been written over the past few days about a spate of new papers by CIRM grantees showing significant differences between reprogrammed iPS cells and embryonic stem cells (see the San Diego Union Tribune, Discover, Technology Review) and CIRM grantee Paul Knoepfler at UC Davis had an insightful blog entry on the topic.

What's causing the stir is the fact that when scientists first reprogrammed skin cells into embryonic-like iPS cells in 2006, those iPS cells seemed like the ultimate solution -- all the power of embryonic stem cells without the embryos. Everybody wins!

Since their introduction, many papers have been published announcing better ways of generating the cells and comparing the cells to their embryonic counterparts. What's emerging is a somewhat complicated story in which there are some clear wins, but also some questions. We reported yesterday and a few weeks ago on some of the wins: iPS cells have been proving themselves ideal for mimicking a disease in a dish.

However, the cells do appear to be significantly different than embryonic stem cells. My colleague Zachary Scheiner in our science office had this to say about the various papers that came out this week:

" There are many similarities between embryonic and reprogrammed stem cells, but a number of recent papers have highlighted differences that could affect the utility of iPS cells for therapies. In one paper, Lister et al. examined a chemical alteration to DNA, called methylation, in a variety of cell types including embryonic stem cells, iPS cells, and adult skin and fat cells. DNA methylation is a normal biological process and helps determine which genes in the DNA get made into proteins in the cell. The DNA in your skin cells, for example, has different methylation than that in your liver cells because those two types of cells need to make different proteins.

Lister et al. found that reprogramming adult skin and fat cells to iPS cells caused hundreds of locations in the genome to have unusual methylation compared to embryonic stem cells. Importantly, these differences remain after the cells are matured into other cell types. This finding suggests that these aberrant DNA modifications could affect the function of cells derived from iPS cells for therapeutic purposes, such as transplantation into patients.

In a complementary paper, Gore et al. examined iPS cells for genetic changes, or mutations, in the DNA code itself, which can have profound effects on the safety of the cells. They found that the process of creating iPS cells introduced an average of six gene mutations per cell line, many more than would be predicted from normal cell culturing. Further, they found that 40% of the mutations discovered were in genes previously found to be mutated in cancers.
Let's review that last sentence: 40% of the mutations discovered in iPS cells were in genes associated with cancer.

In the San Diego Union Tribune, Keith Darce quotes CIRM grantee Jeanne Loring of Scripps Research Institute, who has published several papers showing genetic differences between the two cell types:

" "The big question is, is there anything wrong with this stuff happening? We have no idea."
My colleague Zachary Scheiner summed it up like this:

" Taken together, these two papers raise cautionary flags for researchers seeking to develop cell therapies from iPS cells. However, they also empower these researchers by revealing the types of abnormalities that exist in these cells. Armed with this knowledge, researchers should be better able to assess and assure the safety of iPS cell-derived therapies prior to clinical translation.
The great thing about giving money to smart people (that would be our grantees) is that we can now hope to see papers investigating safety issues that result from these genetic changes, or developing ways of creating iPS cells with fewer anomalies.

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- A.A.

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